

Response to Restriction Requirement
Serial No. 09/657,919
Page 3 of 12

Patent
030727.0035.UTL

Although the conflicting claims are not identical, they are not patentably distinct from each other because the core structure of the cyclic phosphate prodrug overlaps substantially, specifically when the variable Y is oxygen. Additionally, the identity of variable W, W', V, and Z are all substantially overlapping. The examiner notes the major difference between the instant composition claims and the patented claims is in the scope of the heteroatoms attached to the phosphorus in the ring structure. In the instant invention the heteroatoms are selected from oxygen or amine linkages, however the patent limits the heteroatoms to the phosphorus atom to oxygen. The use of this class of compounds to affect a liver related condition is also seen to be obvious in view of claim 174 of the Erion et al. patent. It would have been obvious to the skilled artisan that these compositions of matter and the method for administering the same to affect a liver related condition are indeed *prima facie* obvious and to neglect to advance an obviousness double patenting rejection is to encourage the unjustified or improper extension of the "right to exclude" granted by a patent. (Office Action pp. 3-4)

Although an obviousness-type double patenting determination relies on a comparison with the claims in the Erion *et al.* patent, the obviousness-type double patenting determination parallels the guidelines for an obviousness determination. M.P.E.P. § 804. Therefore, the Examiner bears the initial burden of establishing a *prima facie* case of obviousness-type double patenting. The Applicants respectfully submit that the Examiner has not presented a *prima facie* case of obviousness-type double patenting.

The Applicants respectfully submit that a person of ordinary skill in the art would not find that any claim in this Application is an obvious variation of claims 95-97, 99-172, and 174 of the Erion *et al.* patent. Although the structures of both inventions share an overlapping cyclic phosphonate structure, they differ in terms of M groups. A person of ordinary skill in the art would not find the required chemical modifications from the structures claimed by the Erion *et al.* patent to the structures claimed in the current invention to be obvious.

The Erion *et al.* patent generally claims M groups that are nucleosides and nucleoside analogs that are primarily oncolytic and antiviral compounds. The compounds in the Erion *et al.* patent claims are active in the phosphorylated form. ('662 patent, Col. 17, lines 9-20) The nucleoside compounds of the Erion *et al.* patent are effective in the liver, because they are

Response to Restriction Requirement
 Serial No. 09/657,919
 Page 4 of 12

Patent
 030727.0035.UTL

generally created in the liver and generally not transported out of the liver, just transformed there. Although the specification of the Erion *et al.* patent may not be used to prove obviousness-type double patenting, the portions of the specification supporting the claims may be "considered when addressing the issue of whether or not a claim in the application defines an obvious variation of an invention claimed in the patent." M.P.E.P. § 804.

Here the Detailed Description of the Invention of the Erion *et al.* patent shows that the Erion *et al.* drugs are active in the phosphorylated form.:

The invention is directed to the use of new cyclic phosph(on)ate ester methodology which allows compounds to be efficiently converted to phosph(on)ate containing compounds by p450 enzymes found in large amounts in the liver and other tissues containing these specific enzymes. This methodology can be applied to various drugs and to diagnostic imaging agents. More specifically, the invention is directed to the use of prodrug-esters of highly charged phosphate, phosphoramidate, and phosphonate containing drugs that undergo non-esterase-mediated hydrolysis reactions to produce the phosphate, phosphoramidate, and phosph(on)ate containing compounds. '662 patent, Col. 17, lines 9-20.

In contrast, the compounds of the present invention are not nucleosides and are not known to be active in the phosphorylated form. The compounds of the present invention can be used as oncolytic and antiviral agents, but they may also be useful in treating other diseases. In fact, the compounds of this invention have the ability to leak out from the original location in the hepatocytes. This is noted in the specification in several places including the following:

Cancers outside the liver may also exhibit CYP3A4 activity whereas normal tissue surrounding the tumor is devoid of activity. Tumors that metastasize to the liver from non-P450-expressing organs (e.g. breast) often do not have P450 activity. Prodrugs of the invention, however, are still suitable for treatment of these tumors since the drug is produced in normal hepatocytes and depending on the drug, can diffuse out of the hepatocyte and into the tumor. p. 35, lines 1-6.

Accordingly, the group M represents a group that as part of a compound of formula I enables generation of a biologically active compound *in vivo* by conversion to MH via the corresponding M-

Response to Restriction Requirement
 Serial No. 09/657,919
 Page 5 of 12

Patent
 030727.0035.UTL

PO_3^{2-} , $\text{M}-\text{P}(\text{O})(\text{NHR}^6)_2$, or $\text{M}-\text{P}(\text{O})(\text{O}^-)(\text{NHR}^6)$. The atom in M attached to phosphorus may be O, S or N. The active drug may be MH or a metabolite of M-H useful for treatment of diseases in which the liver is a target organ, including diabetes, hepatitis, liver cancer, liver fibrosis, malaria and metabolic diseases where the liver is responsible for the overproduction of a biochemical end products such as glucose (diabetes), cholesterol, fatty acids and triglycerides (atherosclerosis). Moreover, M-H may be useful in treating diseases where the target is outside the liver in tissues or cells that can oxidize the prodrug. p. 55, lines 9-18.

Selective breakdown of the drug by the liver, since the liver is the site which has the highest levels of the P450 isoenzymes that catalyze the oxidative cleavage of the prodrugs of formula 1, is envisioned to result in high liver drug concentrations. In some cases, the drug will remain predominantly in the liver due to high protein binding or due to metabolic processes (e.g. glucuronidation reactions) that convert the drug to metabolites that are retained by the liver. In other cases, the drug will diffuse out of the liver and enter the blood stream and subsequently other tissues. p. 60, lines 20-26.

As can be seen by looking at the specification of this Application and the Erion *et al.* patent claims, the compounds of the present invention differ from those of the Erion *et al.* patent in terms of the biological activity of the phosphorylated compound. The Erion *et al.* patent claims make it clear that the drug becomes biologically active when it is phosphorylated. Again, this is supported by the specification of Erion *et al.*:

Parent drugs of the form MH, which are phosphorylated to become the biologically active drug are well suited for use in the prodrug methodology of the present invention. There are many well known parent drugs of the form MH which become biologically active via phosphorylation. '662, Col. 28, lines 3-8.

In the present invention, the phosphorylated compounds are biologically inactive, and this is also supported by the specification:

Various kinds of parent drugs can benefit from the prodrug methodology of the present invention. It is preferred that the prodrug phosph(oramid)ate moiety be attached to a hydroxy, amine, or thiol on the parent drug. In many cases the parent drug will have many such functional groups. The preferred group

Response to Restriction Requirement
Serial No. 09/657,919
Page 6 of 12

Patent
030727.0035.UTL

selected for attachment of the prodrug is the group that is most important for biological activity and is chemically suitable for attachment of the prodrug moiety. Thus, the phosph(oramid)ate moiety will prevent the prodrug from having biological activity. An inactive prodrug should limit systemic side effects because higher drug concentrations will be in the target organ (liver) relative to non-hepatic tissues. The amine should have at least one N-H bond, and preferably two. p. 34, lines 6-15.

In addition, as stated in the Detailed Description of the Invention, the present invention is directed toward prodrugs of prodrugs:

The invention is directed to the use of new cyclic 1,3-propenyl phosph(oramid)ate esters which are converted to phosphate, phosphoramidate, or thiophosphate containing compounds by P450 enzymes found in large amounts in the liver and other tissues containing these specific enzymes. The phosphates, phosphoramidates and thiophosphates are then hydrolyzed (by alkaline phosphatase, for example) to produce the free hydroxy, amine, or thiol, respectively. This methodology can be applied to various drugs and to diagnostic imaging agents which contain -OH, -NHR², or -SH functionality. In effect, this methodology provides *a prodrug* (cyclic 1,3-propenyl phosph(oramid)ate esters) *of a prodrug* (phosphate, phosphoramidate, or thiophosphate) *of a drug* (contains -OH, -NHR² or -SH). p. 17, line 24 – p. 18, line 5 (emphasis added).

In view of the fact that the present invention is in effect a double prodrug of a drug that is not active in a phosphorylated form, a person of ordinary skill in the art would not find the claims of the current Application obvious in view of claims 95-97, 99-172, and 174 of the Erion *et al.* patent. Therefore, the Applicants respectfully request withdrawal of the double patenting rejection.

II. THE 35 U.S.C. 103(a)/102(e) REJECTION

Claims 1-49, 65-88, 104-118, and 155-158 have been rejected as being obvious over the Erion *et al.* patent, U.S. Patent No. 6,312,662. The Examiner says:

Response to Restriction Requirement
Serial No. 09/657,919
Page 7 of 12

Patent
030727.0035.UTL

Although the conflicting claims are not identical, they are not patentably distinct from each other because the core structure of the cyclic phosphate prodrug overlaps substantially, specifically when the variable Y is oxygen. Additionally, the identity of variable W, W', V, and Z are all substantially overlapping. The examiner notes the major difference between the instant composition claims and the patented claims is in the scope of the heteroatoms attached to the phosphorus in the ring structure. In the instant invention the heteroatoms are selected from oxygen or amine linkages, however the patent limits the heteroatoms to the phosphorus atom to oxygen. The use of this class of compounds to affect a liver related condition is also seen to be obvious in view of claim 174 of the Erion et al. patent. It would have been obvious to the skilled artisan that these compositions of matter and the method for administering the same to affect a liver related condition are indeed *prima facie* obvious and to neglect to advance an obviousness double patenting rejection is to encourage the unjustified or improper extension of the "right to exclude" granted by a patent. (Office Action pp. 5-6)

The Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness, and until such a showing is made, Applicants are under no obligation to present evidence of non-obviousness. *See In re Piasecki*, 223 U.S.P.Q. 785, 787-88 (Fed. Cir. 1984)(acknowledging that the PTO bears the initial burden of establishing a *prima facie* case of obviousness.). To establish a *prima facie* case, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *See In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable likelihood of success, determined from the vantage point of a skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir 1991). Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *See In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). It is well established that the teachings or suggestions, as well as the reasonable expectation of success, must come from the

Response to Restriction Requirement
Serial No. 09/657,919
Page 8 of 12

Patent
030727.0035.UTL

prior art, not from the applicant's disclosure. *See In re Vaeck*, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991).

As explained above, a person of ordinary skill in the art would not find the invention of the current application obvious in view of the Erion *et al.* patent. The Erion *et al.* patent discloses M groups that are nucleosides and nucleoside analogs that are primarily oncolytic and antiviral compounds. The compounds in the Erion *et al.* patent are active in the phosphorylated form. The nucleoside compounds of the Erion *et al.* patent are effective in the liver, because they are generally created in the liver and generally not transported out of the liver, just transformed there.

In contrast, the compounds of the present invention are not nucleosides and are not known to be active in the phosphorylated form. The compounds of the present invention can be used as oncolytic and antiviral agents, but they may also be useful in treating other diseases. In fact, the compounds of this invention have the ability to leak out from the original location in the hepatocytes.

It is clear that the compounds of the present invention differ from those of the Erion *et al.* patent in terms of the biological activity of the phosphorylated compound. In addition, the present invention is directed toward prodrugs of prodrugs.

It is highly unlikely that a person of ordinary skill in the art would be motivated by the Erion *et al.* patent, which discloses prodrugs of nucleoside and nucleoside analogs, to make a prodrug of a prodrug of a drug MH, which is not a nucleoside. This approach would basically require two transformations to make the drug in the body. There is simply no motivation or suggestion in Erion *et al.* to design a double prodrug of a drug.

In addition, even if a person of ordinary skill in the art was motivated to make the required chemical modifications, that person would not have a reasonable likelihood of success. There is no reason to believe that the substitution of non-nucleoside M groups for the nucleosides and nucleoside analog M groups used in Erion *et al.* would result in compounds that can successfully treat diseases of the liver or metabolic diseases where the liver is responsible for the overproduction of a biochemical end product.

Response to Restriction Requirement
 Serial No. 09/657,919
 Page 9 of 12

Patent
 030727.0035.UTL

In view of the fact that the present invention is in effect a double prodrug of a drug that is not active in a phosphorylated form, a person of ordinary skill in the art would not find the invention of the current Application obvious in view of the Erion *et al.* patent. Therefore, the Applicants respectfully request withdrawal of the 103(a)/102(e) rejection.

III. THE 35 U.S.C. 103(a) REJECTION

Claims 1-49, 65-88, 104-118, and 155-158 have been rejected as being obvious over the Erion *et al.* patent, U.S. Patent No. 6,312,662.

The Examiner believes that the current claims 1-49, 65-88, 104-118, and 155-157 are "drawn to a phosphate containing compound wherein the active agent represented by the variable M is etoposide." (Office Action p. 6). The Examiner also believes that claim 158 "is drawn to a method for treating diseases of the liver using a compound of claim 1." (Office Action p. 6).

The Examiner cites the factors from *Graham v. John Deere*, and then goes on to say:

The Erion patent is seen to disclose compounds wherein a phosphate-containing compound wherein the active agent is intended to affect hyperlipidemic conditions, see claims 95 and 96. In column 32, the compound etoposide is specifically set forth as compounds suitable for conversion to compounds of formula I. The structure of formula I in claim 95 is seen to overlap substantially with the instantly claimed invention. Compounds in which two single bonds of oxygen attached directly to the phosphorus atom form the ring structure of the instant invention must be noted. In column 21, lines 61 through column 22, line 17, the prior art clearly sets forth the use of compounds sharing the same chemical core as that which the applicant claims, for treating liver diseases and associated conditions.

It would have been obvious to one having ordinary skill in this art at the time the invention was made to obtain a cyclic phosphorus containing compound wherein all atoms attached directly to said phosphorus to form a ring are oxygen atoms and the biologically active agent is the saccharide derivative etoposide, because the Erion *et al.* patent discloses same as indicated *supra*. It requires little to find motivation to formulate compositions as applicant claims because the structural core of the prior art compounds represents a species of the broad genus applicant claims in the instant application. The method for treating liver disease or an associated condition is also seen to be disclosed in the prior art

Response to Restriction Requirement
Serial No. 09/657,919
Page 10 of 12

Patent
030727.0035.UTL

patent as set forth *supra* and the invention as claimed is indeed *prima facie* obvious in view of the Erion *et al.* patent. (Office Action pp. 6-7)

As explained above, a person of ordinary skill in the art would not find the invention of the current application obvious in view of the Erion *et al.* patent. Therefore the Examiner has not met his burden of establishing a *prima facie* case of obviousness.

The Examiner specifically refers to the mention of etoposide at Col. 32-Col. 33 of the Erion *et al.* patent as support for his position.

The Applicants respectfully submit that the reference to etoposide is not prior art to the current Application. The statements that the Examiner refers to regarding etoposide were not included in any of the priority applications to the Erion *et al.* patent. These statements were not included until the filing of the application that became the Erion *et al.* patent, on September 8, 1999. This is the same date as the filing of the priority application in this case. Thus, this particular etoposide reference in the Erion *et al.* patent cannot be used as prior art to the present application.

Furthermore, the Applicants disagree with the Examiner's finding that "the structural core of the prior art compounds represents a species of the broad genus applicant claims in the instant application." (Office Action p. 7) As the Applicants have explained above, although the structures of both inventions share an overlapping cyclic phosphonate structure, they differ significantly in terms of M groups.

The Applicants again emphasize that the Erion *et al.* patent discloses M groups that are nucleosides and nucleoside analogs that are primarily oncolytic and antiviral compounds. The compounds in the Erion *et al.* patent are active in the phosphorylated form. The nucleoside compounds of the Erion *et al.* patent are effective in the liver, because they are generally created in the liver and generally not transported out of the liver, just transformed there.

In contrast, the compounds of the present invention are not nucleosides and are not known to be active in the phosphorylated form. The compounds of the present invention can be used as oncolytic and antiviral agents, but they may also be useful in treating other diseases. In fact, the compounds of this invention have the ability to leak out from the original location in the hepatocytes.

Response to Restriction Requirement
Serial No. 09/657,919
Page 11 of 12

Patent
030727.0035.UTL

In view of the above arguments and the fact that the present invention is in effect a double prodrug of a drug that is not active in a phosphorylated form, a person of ordinary skill in the art would not find the invention of the current Application obvious in view of the Enion *et al.* patent. Therefore, the Applicants respectfully request withdrawal of the 103(a) rejection.

CONCLUSION

In conclusion, Applicants respectfully submit that all pending claims are in condition for allowance. The Examiner is invited to contact Applicants' undersigned Representative if it is believed that prosecution may be furthered thereby.

Respectfully Submitted,

Date: 3/4/03

By: Diana L. Bush
Diana L. Bush, Ph.D.
Reg. No. 51,109

Paul, Hastings, Janofsky & Walker LLP
12390 El Camino Real
San Diego, CA 92130-2081
Direct Dial: (858)720-2885
Facsimile: (858)720-2555

Response to Restriction Requirement
Serial No. 09/657,919
Page 12 of 12

Patent
030727.0035.UTL

Marked Up Copy of the Specification

p. 34, lines 6-15:

Various kinds of parent[s] drugs can benefit from the prodrug methodology of the present invention. It is preferred that the prodrug phosph(oramid)ate moiety be attached to a hydroxy, amine, or thiol on the parent drug. In many cases the parent drug will have many such functional groups. The preferred group selected for attachment of the prodrug is the group that is most important for biological activity and is chemically suitable for attachment of the prodrug moiety. Thus, the phosph(oramid)ate moiety will prevent the prodrug from having biological activity. An inactive prodrug should limit systemic side effects because higher drug concentrations will be in the target organ (liver) relative to non-hepatic tissues. The amine should have at least one N-H bond, and preferably two.